Group A Streptococcus
From Basic Science to Clinical Disease

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It is not surprising that the spectrum of group A streptococcal (GAS) infections is changing,[1-8] as history is replete with descriptions of epidemics of rheumatic fever, scarlet fever, poststreptococcal glomerulonephritis, erysipelas, and severe pharyngitis. Although all types of GAS infection may occur simultaneously in a community, the prevalence of each illness fluctuates greatly in a given time period. For example, major epidemics of severe scarlet fever have been well described over the course of several centuries. Similarly, the prevalence of rheumatic fever has changed considerably in the past century and currently has reached a nadir in the western world, but the disease remains a major health problem in developing countries. Finally, the prevalence of streptococcal pharyngitis varies widely at different times of the year in all temperate climates.

Although the factors that govern these fluctuations are poorly understood, it is clear that attack rates vary in a cyclical manner. The span of each cycle cannot be accurately calculated because of inconsistent epidemiologic reporting. For example, in the United States, there have been no objective national data on the prevalence of any GAS infection for the past several decades. On the other hand, the Colindale Laboratory in Great Britain has tracked the prevalence of various M types isolated clinically over the past 20 years.[6] Investigators at the laboratory have shown that following the re-emergence of a given streptococcal M type, its prevalence increases, it becomes the dominant M type, and then its prevalence gradually tapers off. Between 1980 and 1990, M type 1 emerged as the dominant strain, and other M types that predominated in the early 1980s virtually disappeared. Interestingly, M-3 strains were found at a lower, but relatively constant, rate throughout this period.

Conventional wisdom suggests that because a specific opsonic antibody against a given M type affords protection, the acquisition of immunity by a substantial proportion of the population would herald the disappearance of that particular strain in that community. This would seem to explain, at least in part, the rise and fall of the prevalence of various M types documented in Great Britain.[6] In Sweden, however, a remarkable epidemiologic phenomenon occurred between 1985 and 1994 in which M type 1 accounted for more than 70% of all the M types identified in clinical specimens.[8] Such a high prevalence had never before been observed. This phenomenon would be understandable if M-1 had never before been seen in that country, but M-1 strains were not newcomers to Sweden or any other country. In fact, M-1 strains have been associated with scarlet fever, rheumatic fever, and streptococcal pharyngitis since before World War II. The likely explanation is that not all M-1 strains are identical. In support of this notion, it has been demonstrated that the *N*-terminal portion of the M proteins among different M-1 strains may vary.[9]

This observation raises two questions: First, will antibody against one M-1 strain be protective against a different M-1 strain? Second, does a minor alteration in the M protein sequence affect its ability to act as a virulence factor? Although this latter question has not been adequately answered, the fact that M-1 strains remain the most common M type isolated from patients with the streptococcal toxic shock syndrome suggests that such phenotypic heterogeneity does not diminish its virulence.[1,3,4,6-8,10,11]

Although some argue that a clone of M type 1 has emerged that has precipitated the recent upsurge of severe invasive GAS infections, it is clear that various M types, such as M-3, M-4, M-6, M-11, M-12, and M-28, as well as nontypable strains, may also cause the streptococcal toxic shock syndrome.[1,3,4,7,8,10,12] Thus, M typing is a powerful epidemiologic tool, yet the role of the different M proteins in the pathogenesis of the streptococcal toxic shock syndrome is poorly understood. It has been shown that among postpartum women, the absence of opsonic antibody against M-1 was significantly associated with the development of invasive GAS infection.[8] This concept fits well with one well established by Lancefield more than 40 years ago, that type-specific antibody affords protection. In light of the recent data regarding phenotypic heterogeneity among M-1 strains, however, we must now consider whether a "subtype" specific antibody is what is required for protection.

We and others have found a strong association

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ABBREVIATIONS USED IN TEXT

GAS = group A streptococcal
IL = interleukin
SPEA [B, C] = streptococcal pyrogenic exotoxin A [B, C]
TNFα = tumor necrosis factor α

between pyrogenic strains of exotoxin A (SPEA) and the streptococcal toxic shock syndrome in the United States.[1,4,7,11,13,14] Not all strains associated with this syndrome produced SPEA, however, and many did not contain the *SPEA* gene.[1,7,8,11,14] Because all strains of GAS contain the gene for pyrogenic exotoxin B (*SPEB*),[14] it was no more a marker for the toxic shock syndrome than it was for less severe GAS infections.[1,7,8,11] The gene for pyrogenic exotoxin C (*SPEC*), like *SPEA*, is transmitted by bacteriophage, and strains producing SPEC alone have most commonly been associated with mild cases of scarlet fever in modern times. Recently two other pyrogenic exotoxins have been identified. Mitogenic factor, or at least the gene for mitogenic factor, has been found in virtually every strain of GAS by gene probe.[15,16] Thus, its role in the streptococcal toxic shock syndrome is not clear at the present time, and streptococcal superantigen (SSA) has been found in an M-3 strain from Idaho, and its role in pathogenesis awaits further study.[17]

All of these exotoxins, and certain M proteins (M-5), have the ability to act as superantigens, causing T-cell proliferation in vitro.[18] It is theorized that some of the manifestations of the streptococcal toxic shock syndrome may be related to the clonal proliferation of specific T-cell subsets bearing specific Vβ repertoires. In addition, these superantigens are potent inducers of the proinflammatory cytokines tumor necrosis factor α (TNFα), interleukin (IL)-1 and IL-6, and the lymphokines, TNFβ, IL-2, and interferon gamma. Recently the mapping of Vβ expression of circulating T lymphocytes was studied in patients with the streptococcal toxic shock syndrome, and surprisingly, there was no expansion of any T-cell subset.[19] In fact, there was apparent deletion of T cells bearing specific Vβ markers. These deleted subsets did not correlate with markers specific for SPEA, SPEB, SPEC, or streptococcal superantigen. This raises several questions. First, did this work define an as-yet-unidentified superantigen specific for the T-cell Vβ subsets deleted? Second, was T-cell clonal proliferation present earlier in the course, that is, before the clinical manifestations of the toxic shock syndrome were apparent? And, finally, by what mechanism did deletion of the specific T-cell subsets occur? Thus, in humans, the role of the pyrogenic exotoxins has not been established.

There seems to be good evidence that cytokines play an important role in the streptococcal toxic shock syndrome. Cytokines such as TNF, IL-1, and IL-6 have been detected in the blood of patients with this disorder, although like endotoxin-induced shock, the quantities of TNF and IL-1 vary.[20] In mouse and baboon models of invasive GAS infections, high levels of TNFα have been measured.[21] Similarly, the administration of an anti-TNFα monoclonal antibody improved survival, attenuated organ failure, and markedly improved the mean arterial pressure.[21]

Although the pyrogenic exotoxins have been most extensively studied, it is clear that other streptococcal components, such as peptidoglycan, lipoteichoic acid, and streptolysin O, are potent inducers of cytokine production by monocytes and macrophages.[22] In addition, SPEB, by virtue of its protease activity, may release IL-1β from pre-ILβ.[23] Finally, SPEA and streptolysin O interact synergistically to induce IL-1β synthesis from mononuclear cells.[20]

In summary, the group A streptococcus has again demonstrated its ability to cause a variety of clinical infections and complications in humans. A more severe side of its infective potential is currently being seen. It is clear that the complexities of its epidemiology are not understood, and although recent investigations have provided some clues to its pathogenesis, we have little insight into the host factors that determine the clinical type of disease. This organism has a unique predilection for the human host, and its multifarious adaptations have made it a successful human pathogen. Luckily its adaptability has not, as yet, resulted in resistance to β-lactam antibiotics. Future directions should include better epidemiologic studies combined with basic science investigations into pathogenesis.

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